

vanzacaftor/tezacaftor/deutivacaftor (Alyftrek™)

Policy # 00928

Original Effective Date: 06/01/2025

Current Effective Date: 06/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider vanzacaftor/tezacaftor/deutivacaftor (Alyftrek™)† for the treatment of cystic fibrosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) will be considered when the following criteria are met:

- **Initial**
 - Patient has a documented diagnosis of cystic fibrosis; AND
 - Patient is 6 years of age or older; AND
 - Patient has confirmation of at least 1 variant in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is either responsive based on clinical and/or *in vitro* data or results in production of CFTR protein as detected by an FDA-cleared test (See policy guidelines section for full list of responsive mutations); AND
 - Alyftrek will not be used in combination with other disease modifying therapies for cystic fibrosis (i.e., ivacaftor [Kalydeco®]‡, lumacaftor/ivacaftor [Orkambi®]‡, tezacaftor/ivacaftor [Symdeko®]‡, or elexacaftor/tezacaftor/ivacaftor [Trikafta™]‡)
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- **Continuation**
 - Patient has received an initial authorization; AND
 - Patient has experienced a beneficial clinical response from baseline (prior to therapy with a CFTR modulator) as evidenced by improved lung function (for example increased percent predicted forced expiratory volume in 1 second [ppFEV₁]), sweat chloride reduction, reduced pulmonary exacerbations, or weight gain.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) in combination with other disease modifying therapies for cystic fibrosis to be **not medically necessary**.**

Based on review of available data, the Company considers the continued use of vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) when the patient has not had a beneficial clinical response while on therapy to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) when patient selection criteria are not met (except the criteria denoted above as **not medically necessary****) to be **investigational**.*

Policy Guidelines

CFTR Gene Mutations Responsive to Alyftrek

Based on Clinical Data						
A455E	G551D	L1077P	R352Q	S1251N	S945L	W1098C
D1152H	G85E	L206W	R75Q	S549N	V562I	W1282R
F508del	H1054D	M1101K	S1159F	S549R	V754M	Y563N
G1244E	I336K	R1066H				
Based on <i>in vitro</i> Data						
I140- I151dup	D443Y	G1265V	I1398S	M150R	R1283M	S977F
I461insGAT	D443Y;G576 A;R668C	G126D	I148L	M152L	R1283S	S977F;R1 438W
I507_1515de I9	D513G	G1298V	I148N	M152V	R1438W	T1036N
I2055del9	D529G	G1349D	I148T	M265R	R170H	T1053I
I2183A→G	D565G	G149R	I148T;H6 09R	M348K	R248K	T1057R
I2851A/G	D567N	G149R;G576 A;R668C	I175V	M394L	R258G	T1086A
I293A→G	D572N	G178E	I331N	M469V	R297Q	T1086I
I3007del6	D579G	G178R	I336L	M498I	R31C	T1246I
I3131delI5	D58H	G194R	I444S	M952I	R31L	T1299I
I3132T→G	D58V	G194V	I497S	M952T	R334L	T1299K
I3141del9	D614G	G213E	I502T	M961L	R334Q	T164P
I3143del9	D651H	G213E;R668 C	I506L	N1088D	R347H	T338I

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314del9	D651N	G213V	I506T	N1195T	R347L	T351I
3195del6	D806G	G226R	I506V	N1303I	R347P	T351S
3199del6	D836Y	G239R	I506V;D 1168G	N1303K	R352W	T351S;R8 51L
3331del6	D924N	G253R	I521S	N186K	R516G	T388M
3410T→C	D979A	G27E	I530N	N187K	R516S	T465I
3523A→G	D979V	G27R	I556V	N396Y	R553Q	T465N
3601A→C	D985H	G314E	I586V	N418S	R555G	T501A
3761T→G	D985Y	G314R	I601F	N900K	R560S	T582S
3791C/T	D993A	G424S	I601T	P1013H	R560T	T604I
3850G→A	D993G	G437D	I618N	P1013L	R600S	T908N
3978G→C	D993Y	G451V	I618T	P1021L	R668C	T990I
4193T→G	E1104K	G461R	I807M	P1021T	R709Q	V1008D
546insCTA	E1104V	G461V	I86M	P111L	R74Q	V1010D
548insTAC	E1126K	G463V	I980K	P1372T	R74Q;R297Q	V1153E
A1006E	E116K	G480C	K1060T	P140S	R74Q;V201M; D1270N	V11I
A1025D	E116Q	G480D	K162E	P205S	R74W	V1240G
A1067P	E1221V	G480S	K464E	P439S	R74W;D1270N	V1293G
A1067T	E1228K	G500D	K464N	P499A	R74W;R1070W ;D1270N	V1293I
A1067V	E1409K	G545R	K522E	P574H	R74W;S945L	V1415F
A107G	E1433K	G551A	K522Q	P5L	R74W;V201M	V201M
A1081V	E193K	G551R	K951E	P67L	R74W;V201M; D1270N	V232A
A1087P	E217G	G551S	L1011S	P750L	R74W;V201M; L997F	V232D
A120T	E264V	G576A	L102R	P798S	R751L	V317A
A1319E	E282D	G576A;R668 C	L102R;F 1016S	P988R	R75L	V322M
A1374D	E292K	G576A;S1359 Y	L1065P	P99L	R75Q;L1065P	V392G
A141D	E384K	G622D	L1065R	Q1012P	R75Q;N1088D	V456A
A1466S	E403D	G622V	L1227S	Q1100P	R75Q;S549N	V456F
A155P	E474K	G628A	L1324P	Q1209P	R792G	V520F
A234D	E527G	G628R	L1335P	Q1291H	R792Q	V520I
A234V	E56K	G85V	L137P	Q1291R	R810G	V562I;A1 006E
A238V	E588V	G91R	L137R	Q1313K	R851L	V562L
A309D	E60K	G930E	L1388P	Q1352H	R933G	V591A
A349V	E822K	G970D	L1480P	Q151K	S1045Y	V603F
A357T	E92K	G970S	L159S	Q179K	S108F	V920L
A455V	F1016S	G970V	L15P	Q237E	S1118F	V920M

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A457T	F1052V	H1079P	L15P;L1 253F	Q237H	S1159P	V93D
A462P	F1074L	H1085P	L165S	Q237P	S1188L	W1282G
A46D	F1078S	H1085R	L167R	Q30P	S1235R	W202C
A534E	F1099L	H1375N	L210P	Q359K/T360 K	S1255P	W361R
A554E	F1107L	H1375P	L293P	Q359R	S13F	W496R
A559T	F191V	H139L	L320V	Q372H	S13P	Y1014C
A559V	F200I	H139R	L327P	Q452P	S158N	Y1032C
A561E	F311del	H146R	L32P	Q493L	S182R	Y1032N
A566D	F311L	H147del	L333F	Q493R	S18I	Y1073C
A613T	F312del	H147P	L333H	Q552P	S18N	Y1092H
A62P	F433L	H199Q	L346P	Q98P	S308P	Y109C
A72D	F508C	H199R	L441P	Q98R	S341P	Y109H
A872E	F508C;S1251 N	H199Y	L453S	R1048G	S364P	Y109N
c.1367_1369 dupTTG	F508del;R143 8W	H609L	L467F	R1066C	S434P	Y122C
C225R	F575Y	H609R	L558F	R1066G	S492F	Y1381H
C491R	F587I	H620P	L594P	R1066L	S50P	Y161C
C590Y	F587L	H620Q	L610S	R1066M	S519G	Y161D
C866Y	F693L(TTG)	H939R	L619S	R1070P	S531P	Y161S
D110E	F87L	H939R;H949 L	L633P	R1070Q	S549I	Y301C
D110H	F932S	H954P	L636P	R1070W	S557F	Y517C
D110N	G1047D	I1023R	L88S	R1162L	S589I	Y569C
D1152A	G1047R	I1027T	L927P	R1162Q	S589N	Y89C
D1270N	G1061R	I105N	L967F;L 1096R	R117C	S624R	Y913C
D1270Y	G1069R	I1139V	L967S	R117C;G576 A;R668C	S686Y	Y913S
D1312G	G1123R	I1203V	L973F	R117G	S737F	Y919C
D1377H	G1173S	I1234L	L997F	R117H	S821G	
D1445N	G1237V	I1234Vdel6aa	M1101R	R117L	S898R	
D192G	G1244R	I125T	M1137R	R117L;L997F	S912L	
D192N	G1247R	I1269N	M1137V	R117P	S912L;G1244V	
D373N	G1249E	I1366N	M1210K	R1239S	S912T	
D426N	G1249R	I1366T	M150K	R1283G	S955P	
D426N	G1249R	I1366T	M150K	R1283G	S955P	

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Background/Overview

Cystic fibrosis (CF) is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations in a gene that encodes for a protein called CFTR that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes.

Alyftrek is a combination of three drugs, vanzacaftor, tezacaftor, and deutivacaftor. Vanzacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR to increase the amount of CFTR protein delivered to the cell surface. Deutivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. These drugs work together to increase CFTR activity in patients with a responsive mutation. If a patient's mutation status is not known, an FDA-cleared cystic fibrosis mutation test should be used to determine whether a CFTR mutation is present. Alyftrek is supplied in fixed dose combination tablets with dosing based on the patient's age and weight. In contrast to other disease modifying therapies for CF, Alyftrek may be dosed once daily with a fat-containing food.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Alyftrek was approved in December 2024 for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene. In 2026, the label was updated to state that patients who have at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of CFTR protein.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Alyftrek in patients aged 12 years and older with cystic fibrosis (CF) who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene was evaluated in two 52-week randomized, double-blind, active-controlled trials comparing Alyftrek and a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA) (Trial 1 and Trial 2). The two trials enrolled a total of 971 patients aged 12 years and older with CF who have at least one *F508del* mutation or other ELX/TEZ/IVA-responsive mutations in the *CFTR* gene. Because patients in Trial 1 and Trial 2 would receive ELX/TEZ/IVA, patients with a history of intolerance to ELX/TEZ/IVA were excluded from these trials.

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Trial 1 enrolled patients with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that was not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function mutation). A total of 398 patients with CF aged 12 years and older received a daily oral dosage of ELX/TEZ/IVA (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening) during a 4-week run-in period and were then randomized to receive Alyftrek (total once daily oral dosage of vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg) or ELX/TEZ/IVA (same dosage as in the run-in period) during the 52-week treatment period. After the 4-week run-in, the mean ppFEV1 at baseline was 67.1 percentage points (range: 28.0, 108.6) and the mean sweat chloride at baseline was 53.9 mmol/L (range: 10.0 mmol/L, 113.5 mmol/L).

Trial 2 enrolled patients with CF who had one of the following genotypes: homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to ELX/TEZ/IVA with no *F508del* mutation. A total of 573 patients with CF aged 12 years and older received a daily oral dosage of ELX/TEZ/IVA (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening) during a 4-week run-in period and were then randomized to receive Alyftrek (total once daily oral dosage of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg) or ELX/TEZ/IVA (same dosage as during the run-in period) during the 52-week treatment period. After the 4-week run-in, the mean ppFEV1 at baseline was 66.8 percentage points (range: 36.4, 112.5) and the mean sweat chloride at baseline was 42.8 mmol/L (range: 10.0 mmol/L, 113.3 mmol/L).

In both trials, the primary endpoint evaluated non-inferiority in mean absolute change in ppFEV1 from baseline through Week 24 and a key secondary endpoint evaluated the mean absolute change from baseline in sweat chloride through Week 24 in the Alyftrek and ELX/TEZ/IVA treatment groups. In Trial 1, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (95% CI: -0.7, 1.1) in absolute change in ppFEV1 from baseline through Week 24 compared to ELX/TEZ/IVA. In Trial 2, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (95% CI: -0.5, 0.9) in absolute change in ppFEV1 from baseline through Week 24 compared to ELX/TEZ/IVA.

As the lower bounds of the 95% CI of the LS mean difference in absolute change from baseline in ppFEV1 through Week 24 were greater than -3.0 percentage points (the pre-specified non-inferiority margin) in Trial 1 and Trial 2, these results demonstrate non-inferiority of Alyftrek to ELX/TEZ/IVA.

References

1. Alyftrek [package insert]. Vertex Pharmaceuticals, Inc. Boston, MA. Updated March 2026.

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05/01/2025 Medical Policy Committee review

05/13/2025 Medical Policy Implementation Committee approval. New policy.

05/07/2026 Medical Policy Committee review

05/13/2026 Medical Policy Implementation Committee approval. Updated to include new mutations FDA approved for treatment with Alyftrek. Added continuation pathway for members with previous approval.

Next Scheduled Review Date: 05/2027

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.